IRRADIATION IN THE LYMPHOMATOID DISEASES*

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THE TERM lymphomatoid diseases embraces an extremely complex collection of morbid and mostly lethal processes. It is outside of the scope of this paper to discuss the few facts and the many theories concerning their causes, or to portray the wide scope of the pathologic changes which they may produce. There is no part of the human body entirely exempt from the possibility of being affected directly or indirectly by these diseases, and there is no age entirely immune from them. They concern therefore, every practitioner of medicine.

Even within the scope of any one of the so-called entities, such as Hodgkin's disease, variations are so great that each case becomes an individual problem for treatment. Yet they do have one thing in common in connection with treatment, and that is that irradiation by Roentgen rays or radium continues to be the single most effective method.

These diseases were among the first to be treated by irradiation, and even with the earliest crude techniques showed some remarkable responses. Yet they are so variable and unpredictable that their treatment by irradiation has remained an art rather than a science, to a degree greater than is true for many of the malignant tumors. In the treatment of some types of cancer, radiation is becoming one of the tools of the surgeon, used much as he might apply the knife or cautery. In malignant tumors affecting restricted parts of the body, for example epitheliomas of the lip, tongue, hypopharynx, skin and cervix, the radiant energy of radium and x-rays may be applied in a highly accurate manner, with rigid specifications of portal shape and size, direction of beam, amount and frequency of dose. Thus, the new type of specialist, the surgeon-radiologist, can develop a fairly standard technique, often combining a surgical procedure with a routine of irradiation that for a given type of cancer may be allowed to remain fairly fixed for a time long enough to permit

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judgment of results.

In the group of lymphomatoid diseases on the other hand, because of their great variations, it is hardly possible to devise a general routine, except perhaps for some of the commoner forms of local lesions, such as tonsillar lymphosarcoma, or Hodgkin's disease restricted to one or two groups of nodes. Yet the problem of determining the optimum technique of irradiation for these local lymphomatoid lesions is difficult. The ease with which regressions are secured by small doses may lead to a false sense of accomplishment, where much larger doses would be needed to effect actual sterilization of the disease. On the other hand, with large doses one may use up the patient's tolerance of radiation in producing regression of one lesion, only to find that other foci soon appear, and then the patient is less well able to withstand further irradiation.

Since we cannot hope to discuss all the possible variations of these diseases and consequent modifications of treatment even solely from the aspect of irradiation, let us therefore take up one by one the commoner types and indicate certain general plans of treatment. We must in advance recognize that cases must be individualized and that a given case may not fit neatly into these plans. We must also recognize that techniques of different workers vary considerably; that in these diseases, which are usually rather radiosensitive, widely different techniques may seem to give about equally good results; and that judgment about the value of a given technique is most difficult in such variable disease processes.

What I shall do here is to outline roughly our current preferences in modes of irradiation, with no claim that these methods are the best. There is no time here to discuss differential diagnosis, so we must assume in general that the diagnosis has been established, by biopsy if possible, and this we are doing routinely.

At this point we may consider briefly the types of radiation suitable for the treatment of these diseases. Beginning with Roentgen rays we have:

1. Low voltage Roentgen rays generated at or about 100,000 volts, suitable only for superficial lesions. These may be used unfiltered for very superficial lesions, or up to 4 or 5 millimeters of aluminum filter may be employed in order to screen out the longer, less penetrating wave-lengths and thus give a type of radiation suitable for lesions of some thickness on, in, or close under the skin.

2. Intermediate voltage Roentgen rays, generated at 140,000 to 160,000 volts, filtered by 3 to 6 millimeters of aluminium. Some workers prefer this type of irradiation even for deep seated lesions—rather illogically, I think, because there is too much effect on the skin and overlying tissues in proportion to what reaches deep parts.

3. High voltage Roentgen rays, usually generated at about 200,000 volts and filtered by 0.5 millimeters of copper or its equivalent. This gives adequate penetration to reach deep parts, and by increasing the target skin distance up to 70 or 100 centimeters or more a quite satisfactory depth dose is obtained without undue effect on the skin.

4. Super-high voltage Roentgen rays generated at 700,000 to 1,000,000 volts or more are probably entirely superfluous in the treatment of the lymphomatous diseases.

When low voltage and high voltage Roentgen apparatus is available, I see no great necessity for radium in the treatment of these diseases, except that extremely rarely there may be an indication for interstitial implantation of radon seeds or needles. Anything that can be done in this field by external application of the gamma rays of radium apparently may be done just as effectively and often more conveniently by Roentgen rays. We do at times use the 4 gram radium pack for external irradiation in place of the high voltage x-rays but not as a rule by preference.

Hodgkin's Disease

Given a case with an established diagnosis of Hodgkin's disease, two questions must be answered as well as possible before planning treatment. First, how extensive is the disease? Second, how acute a process does it seem to be? These questions can only be answered by a careful survey of the case, including history, physical examination, and roentgenographic studies. If, in a patient with very slight or no constitutional symptoms the disease seems to be limited to one group of nodes, as in the neck, one is probably justified in irradiating that area heavily in the hope of complete sterilization. At present we might give such a field 200 r daily or every other day to a total of 2000 r or more. Yet a word of caution at this point: experience in observing large numbers of cases of this disease suggests strongly that such a group of external nodes, apparently the only focus of the disease, is actually only an external sign of a process that gained entry to the body somewhere within the drain-

age territory of those nodes, and that therefore we must be on our guard against the possibility that the disease is already present elsewhere. Especially suspect are cases with a group of nodes at the base of the neck, in the axilla, or in the groin. Such cases call for careful examination of the chest and abdomen. When no internal focus can be found to account for the spread of disease to such an external group of nodes it may well be assumed nevertheless that the *noxa* of the disease, whatever its nature may be, has gained entry into the body at the appropriate internal site and has passed on, probably, however, leaving minimal undetectable traces internally. Therefore, in such situations the question always arises whether one should not give some treatment to the appropriate internal sites. For example, with a group of nodes situated at the base of the neck, in the position of the node of Virchow, even the absence of demonstrable disease in mediastinal or retroperitoneal territory would not exclude from our minds the advisability of giving some treatment to those regions. We do so in many cases but, because of the absence of demonstrable disease in those fields, we tend to give considerably smaller doses than we do to the known focus. We hope that the internal foci may actually be minimal and that smaller doses will serve at least to hold the process in check. We fear that larger doses might too greatly depress the patient's reserves and thus prevent us from giving full treatment if some other definite focus does appear.

To go back for a moment to the treatment of the mass of external nodes, I am by no means certain that the divided dose method of say 200 r every other day to a total of 2000 r is preferable. The dose of 200 r is about the upper limit of a single dose in the hands of most workers. However, some years ago we were giving such cases single doses of 400 to 600 r repeated at varying intervals for a few times. Some of the longest survivors we have had were treated by these fewer but larger doses, and therefore at the Fifth International Congress of Radiology in Chicago last year I ventured to raise the question whether such a method might not be preferable at least in some cases.

Many cases of Hodgkin's disease when first seen present more than one area requiring treatment, but are not yet in an advanced stage. In these cases each field is usually treated by 200 to 300 r every second or third day to a total of 1000 to 1200 r a field. Usually good regression will promptly follow such treatment.

Even cases that are far advanced may be greatly helped by judicious

irradiation. If severely anemic, such patients may be temporarily strengthened by transfusions so that they will better withstand treatment and obtain more good from it. When there are many areas of disease we usually do not try to treat all of them in one course, but select the larger and more important foci, giving them doses chosen empirically according to the bulk and depth of the lesions, and according to the condition of the patient. Some areas may receive 200 to 300 r two to five times at daily to weekly intervals, others about 400 r once. Then we may wait for three or four weeks, to give the patient a chance to get the benefit of this partial treatment. If we have been intelligent in our choice of areas and dosage, improvement may far exceed expectations, and then we have a patient better able to go on with further treatment. Literally, at times, patients with far advanced Hodgkin's disease seem to be pulled back from the brink of the grave by such measures, though at times our choice is not correct, or the disease is even worse than we thought, and we fail.

In some cases with widespread disease it may be well to include large fields such as the entire mediastinum, or the entire central abdomen or even greater sections of the trunk in single beams of radiation used at long target skin distances. Rather routine irradiation of large body fields is advocated particularly by Sluys of Belgium, Gilbert of Switzerland and Desjardins of the Mayo Clinic. I prefer to avoid routines and to choose areas according to the indications of the particular case.

Instead of irradiating the body in huge sections one may arrange the apparatus so that all or nearly all of the body may be irradiated at one time either in short individual sittings as is done in Europe and in a few centers in America, or at low intensity and continuously for days as we have done at Memorial Hospital in the unit named for Doctor Heublein, who suggested the latter method. In Hodgkin's disease irradiation of the entire body is used at Memorial Hospital only in small doses in selected cases and as a supplement to local irradiation. One cannot expect the body to tolerate enough exposure to radiation distributed simultaneously over its whole surface to produce satisfactory regression of bulky masses of granulomatous tissue. Yet, when the local masses and infiltrations have been treated we find in selected cases that by supplementing their treatment by small doses of general body irradiation, one gains frequently a tonic effect, with increase of weight and sense of well being, and freedom from recurrence of signs of disease activity for periods longer

than would otherwise be expected. We must freely admit that this statement is based on observation of numbers of cases, and that it is hardly possible to prove it by statistics. Even if some years from now unusually good survival figures appear among cases treated by general irradiation, one would have to take into consideration also the belief that the methods of local irradiation in the same cases had probably been more efficient. It has not seemed fair to restrict the treatment of any of these patients to general irradiation to see what it alone could do. Whether using general or local irradiation due regard must be had for the patient's tolerance, as judged both by his general state and by his blood count. If the white cell count becomes too low, say about 3000, it is usually best to suspend treatment for a time. However, it is important to point out that in some cases, in which no radiation has been used, a leukopenia will be found. As a rule one may proceed with irradiation in such cases, for it is probable that the low white cell count is caused by the disease, and that irradiation may actually be followed by a rise of the count to normal.

Hilar Tuberculosis and Hodgkin's Disease

In recent years several cases have presented themselves in which it has been very difficult to make a differential diagnosis between hilar tuberculosis and Hodgkin's disease or possibly lymphosarcoma. These are cases in which the Roentgen film shows distinct enlargement of hilar and tracheobronchial nodes of a pattern like that seen in the childhood type of tuberculosis, and in which no enlarged external nodes are available for biopsy. In such cases a negative tuberculin test is regarded as strongly suggestive that the process may be Hodgkin's disease, and accordingly that it may be safe to proceed with irradiation of the mediastinum and hilar nodes. It seems best to begin treatment cautiously, however, in order to test the response.

If, after a month or two a slight regression can be found, and if there has been no unfavorable reaction, it is considered safe to proceed with intensive irradiation, as for Hodgkin's disease.

As for results, we find 17 per cent of patients with histologically verified Hodgkin's disease surviving for five years or longer after treatment was begun. Certain workers report considerably higher five year survival figures than these. I feel that in such series there must have been a selection of cases accepted for treatment. Our figures apply to all cases coming to us in which the diagnosis was proved microscopically.

We reject only moribund patients and those who are under treatment elsewhere and come without permission of the physicians who are treating them. At one time recently we counted twenty-two patients living over five years, and we have now one patient who has survived over seventeen years. She was seemingly free of disease for about fifteen years but developed a mediastinal recurrence a few months ago. This was treated with fairly good response and she is still in good condition.

The most important factor of all in the treatment of Hodgkin's disease, or any of the lymphomatous diseases, is close vigilance for earliest signs of new foci or recurrences. Increased attention to the possibility of lesions of the lungs, bones, deep lymph node areas, nerve roots, spinal canal, and other tissues, leads to earlier detection, or to justified assumption of need for treatment of these parts, and thus to improved palliative results. Increased attention to such supportive measures as transfusions, iron, vitamins, and a general regime as for tuberculosis rewards us with better responses to irradiation and prolonged, more comfortable survival of our patients.

Lymphosarcoma

If in a case of lymphosarcoma the disease is apparently localized in one field, aggressive irradiation is justified in an attempt to cure. Usually such attempts fail, but there is a fair percentage of salvage among such cases, for long periods, if not actual cures. Yet here again we are dealing with variable, unpredictable processes and cases that seem bad may do well, while those that delight us by early complete regression may soon dismay us by the rapidity with which their disease returns and spreads.

In younger individuals, cases beginning as lymphosarcoma, sometimes apparently atypical and seemingly hardly more than an inflammatory process, regressing remarkably well under irradiation, may then rapidly develop a full blown picture of acute leukemia.

In cases of localized lymphosarcoma in which there appears to be a chance to secure complete sterilization, I feel that it may be a mistake to limit the size of the port to an area just large enough to include the palpable tumor, and to protract the treatment by giving small fractional doses daily. In this very cellular disease, tending to infiltrate widely, I believe it preferable to use ample ports and to give larger doses at a time. This is in contrast to the generally used procedure of small doses of low intensity repeated twice a day, daily or every other day to the same

port until a large total dose is attained – sometimes an epidermicidal dose. Some advocate large ports, others would treat lymphosarcoma as they do epidermoid carcinoma by ports kept as small as possible so as to include only the demonstrable part of disease. This is following the principle of treating cancer only where you find it, a principle which needs modification when we deal with lymphosarcoma. Yet we are finding that reticulum cell lymphosarcoma is not always nearly as radiosensitive as was once believed. When we find a case of localized lymphosarcoma that is relatively radioresistant it is probably better to use the protracted divided dose method, as in carcinoma, so that a much larger total dose can be given. In such a case I feel it would be advisable to restrict ports as much as possible for two purposes, first, to spare the patient the effects of as much irradiation of extraneous tissue as possible, and, second, to permit an increase of the dose to the tumor.

When a patient with lymphosarcoma has several widely scattered areas of the disease, obviously one must plan for the best palliation, rather than an attempt to cure. It then becomes a matter of proper choice of areas to be treated first, of individual and total dosage and the intervals between doses. In cases with widespread lymphosarcoma the use of the larger individual doses permits a more rapid coverage of most of the disease, while the protracted small dose method would necessitate a hopelessly long program. Just in this type of case in which the advocates of rigid adherence to that rule of treating cancer where you find it, using small ports and protracted dose methods, would tend to give up and say that such a case is better not treated at all, may be found some of the most worth while results of irradiation in palliation.

Results in Lymphosarcoma

Of 132 patients treated, 1918 to 1933, inclusive, in whom results can be determined, there were twenty-one or 15.9 per cent, who survived five years or longer. Five of these died after five years, while two are living over five years with evidence of disease, so that there are fourteen, or 10.6 per cent who survived five years or longer and who had been free of evidence of disease for six months, and in many cases much longer, ever since the regression that followed the first course of treatment.

Mycosis Fungoides

The superficial tumors and plaques of infiltration of the skin in this

disease are usually very radiosensitive in the beginning, and may yield readily to relatively small doses of low voltage x-rays. However, in many cases there is such widespread involvement of the skin that adequate treatment of all the disease would require more radiation than the patient could tolerate, so that each course of treatment must be restricted to the lesions that are most troublesome or threatening at the time. In later stages the recurrences that may appear in previously irradiated fields may be rather resistant, and lesions may appear in lymph nodes, bones, lungs and other viscera, requiring palliative treatment as for like lesions of advanced Hodgkin's disease or lymphosarcoma.

The Leukemias

In the treatment of leukemia by irradiation it is quite important to gauge the degree of acuteness or chronicity of the process clinically as well as hematologically. No sharp line of demarcation exists between acute and chronic forms but the more acute cases must be irradiated, if at all, with great caution. Even the more chronic cases may be greatly harmed by overenthusiastic treatment. Undoubtedly some leukemics have been killed by radiation effects. Yet judiciously applied radiation can be of benefit even in some cases apparently very acutely ill, and seemingly almost moribund.

It is especially in chronic myelocytic and chronic lymphocytic leukemia that irradiation plays a great part in bringing about restoration of the patient, for periods of varying length, to comparative or apparently complete health and economic usefulness. While statistics seem to show not more than a few months, possibly, of prolongation of life on the average, as compared with untreated cases, yet it seems evident that in some cases the inevitably fatal termination is considerably postponed by irradiation.

Chronic Lymphocytic Leukemia

The typical case of chronic lymphocytic leukemia presents a symmetrical general enlargement of external lymph nodes, commonly with some enlargement of liver and spleen and often with obvious enlargement of retroperitoneal nodes. The blood count may be typically leukemic, subleukemic or aleukemic.

In the typical case our preference is to irradiate first the external node masses, that is, each side of the neck, each axilla, and each groin. Each

such mass is given 100 to 300 r high voltage x-rays once, one area being treated at a time, and the patient being treated at intervals of one to three days depending on his condition. We then wait a few weeks, as a rule, to observe the effect on these external readily palpable masses, and the effect on the blood. Such a test cycle of treatment may be followed by considerable regression of the enlarged nodes and usually by a marked favorable change in the blood count. Anemia may disappear, the white cell count, if high, may fall to nearly normal, while the differential count may show a reversal of the polynuclear: lymphocyte ratio to nearly normal.

Further treatment then depends on the condition of the patient. If his blood count is nearly normal and if he has no marked internal masses of nodes or marked enlargement of spleen or liver it may seem best to withhold treatment until such time as the blood count or signs of leukemic infiltration in some area reveal the need for more treatment.

Unless some special feature appears, ordinarily the next course of irradiation is given to the mediastinal and retroperitoneal nodes. By taking a zone about 10 centimeters wide extending along the midline axis of the trunk, anteriorly and posteriorly, and dividing it into an upper, middle and lower third, one can irradiate the main bulk of these deep nodes. To each of these six portals (three anterior and three posterior) is given 100 to 300 r of high voltage x-rays. The individual doses and the intervals between them are chosen according to the condition of the patient.

Subsequent courses of treatment may consist of repetitions of these cycles to external or internal nodes, or both; or particular fields such as liver or spleen or deep inguinal and iliac nodes may demand special attention. The aleukemic forms are treated in the same way. In these cases, of course, the blood count is of less value, and one must depend largely on the responses of the known foci of disease. It would be quite misleading to gain an impression from this description of technique that a rigid routine is followed. Each case must be individualized and by no means all cases are treated in this way. For example, in the so-called splenic type of lymphocytic leukemia in which there is a large spleen with but little or no enlargement of lymph nodes, the treatment should begin by irradiation of the spleen.

Irradiation of the entire body has seemed to work very well in chronic lymphocytic leukemia and in some cases we choose to begin

the treatment by this method, and to rely mainly on it, using local irradiation rather as a supplement to care for especially prominent masses or infiltrations.

In the rare cases of lymphocytic leukemia in which no enlargement of liver, spleen, or lymph nodes can be found, one would naturally think of general irradiation as a logical procedure.

The emphasis, then, in the treatment of chronic lymphocytic leukemia is first on irradiation of lymph node areas, and second on irradiation of other foci of lymphocytic infiltration, wherever found. About 9 per cent will show a survival of five years or longer after treatment is begun as against the average survival of about two years, and some patients will live ten to twelve years or longer.

Chronic Myelocytic Leukemia

The typical case of this disease presents an enlarged spleen, sometimes of huge dimensions, frequently some enlargement of the liver, and as a rule practically a total absence of signs of enlargement of lymph nodes. The general run of experience indicates that best results, at least in the beginning, are obtained by irradiation of the spleen. This may be done by various methods. At Memorial Hospital we commonly use high voltage x-rays to large ports anteriorly and posteriorly over the spleen, giving 25 to 100 r at a sitting and treating daily or every other day to a total of about 300 r over each of the two ports. In some cases the radium pack is used, giving 2000 milligram hours or less at a sitting, at a radium skin distance of 10 centimeters, to a total of 6000 milligram hours anteriorly and posteriorly.

Such a course of irradiation may be followed by a transient increase in the leukocytosis, but in general, in about a month, a striking improvement will be found in the patient. He may gain weight, lose symptoms, present a marked shrinkage of the spleen, so that in some cases it may no longer be palpable, and his blood count may be restored so nearly to normal that it would be difficult to make a diagnosis of leukemia. In 3 weeks there may be an increase of a million red cells in the count.

Danger lies in overdosage of the more acutely ill patients. When external lymph nodes are enlarged, they may portend a more acute course. Signs of hemorrhagic tendency are danger signals, and indicate caution. Yet this bleeding tendency may disappear after irradiation.

Most of the writers state that it is advisable to be content to reduce

the white cell count to 20,000 or 30,000. If, however, our first cycle of treatment can succeed in bringing the count down to a normal level, I believe the patient as a rule will have a more nearly complete restoration to health for the time being and a longer interval before another course of treatment becomes necessary.

The blood count ordinarily gives the first sign that the disease is becoming active again and should be taken at intervals of seldom more than three weeks, at least at first. Further treatment is very much a matter of individualization. Some cases may carry on for years in response to repeated courses of irradiation given only to the spleen when it re-enlarges. In other cases special features arise, demanding special treatment. In some cases the blood count deteriorates again to a degree demanding more treatment at a stage when liver and spleen remain reduced to nearly normal size. At such times we consider either irradiation of the bones, especially spine, sternum, and proximal ends of long bones, or irradiation of the entire body in small dosage. We are especially likely to think of irradiation of the bones in cases in which pains are felt about the bones and joints.

In some cases the spleen fails to shrink satisfactorily after a few cycles of treatment have been given to the spleen; and even after further irradiation it remains large and firm. Some authors report shrinkage of these refractory spleens after irradiation of the entire body. We have not confirmed these observations, but see no reason to doubt that such an effect may be possible. Adjuvant methods of treatment such as administration of arsenic, heliotherapy and transfusions are regarded as outside the scope of this paper.

Results. Sooner or later every case becomes refractory to treatment. On the average these patients die in about two or three years after treatment is begun. Some survive exceptionally long periods, even up to fifteen or twenty-five years, but in these cases one feels that there is some exceptional factor promoting longevity and that the treatment may have had relatively little to do with the long survival. Only a small percentage (about 6 per cent) of the patients with myelocytic leukemia survive over five years after beginning treatment. The chief value of irradiation in this disease lies in the fact that it can bring about remissions repeatedly, to an extent which would not ordinarily occur, so that the patient, during his remaining span of life, short though it may be, enjoys periods of comparative health which otherwise he could not have.

Polycythemia Vera

Polycythemia vera or erythremia may be regarded as an analogue of myelocytic leukemia, that is, as a disease in which the red cell series rather than the granulocytic series is stimulated to increased activity. It has been advocated that in erythremia the enlarged spleen should be regarded as serving a protective function and that therefore it should not be irradiated; that, on the contrary, all the treatment should be directed to the bone marrow, which is the primary seat of the disease. The same argument might seem to apply to myelocytic leukemia, yet general experience has shown that in that disease irradiation of the spleen as a rule gives results superior to those obtained by treatment of the bones. However, in treating erythremia by local irradiation we do now as a rule, direct our radiation to the bones (spine, sternum and ends of long bones). Sgalitzer and others claim excellent results in erythremia by systematic total body irradiation. Sgalitzer reported good results in forty-two of forty-four cases, stating that in the recurrences one and one-half to five and one-half years later he obtained just as good response as in the first cycle of total irradiation, and that these recurrences took place much later than after the expensive, time-consuming cycles of local irradiation of multiple fields.

However, in this field there are certain cases termed erythroleukemia in which usually the dominating features at first are those of erythremia, but in which the spleen may be unusually large, the white cell count unusually high and the percentage of myelocytes in the blood count unusually great. In such cases the red cell count may fall after some months, so that instead of polycythemia the patient develops an anemia and then the features of myelocytic leukemia may begin to predominate. In such cases we find that treatment of the spleen may be more efficacious than treatment of bones in relieving symptoms.

Summary

In summary, the problems of treatment of the lymphomatoid diseases are many and complex, by reason of the great diversity of lesions in this group of maladies. Here are presented the main principles which currently seem to me best to follow in caring for the more typical forms by means of irradiation.

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